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Review

Graves' disease, thyroid nodules and thyroid cancer

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Introduction

Thyroid cancer associated with either Graves' disease or other forms of thyrotoxicosis, after the initial description in 1948 (Pemberton & Black, 1948), has been reported in many other patients, identifying a subgroup of thyroid tumours requiring a distinct approach to clinical management (Paul & Sisson, 1990).

The coexistence of thyrotoxicosis and thyroid cancer includes various pathological conditions that can be categorized as follows:

- Thyroid cancer associated with thyrotoxicosis caused by: (i) Graves' disease; (ii) toxic multinodular goitre (TMG); (iii) autonomously functioning thyroid adenoma (AFTN).
- Thyroid cancer causing thyrotoxicosis by: (i) thyroid hormone hyperproduction by primary or secondary thyroid cancer overstimulated by anti-TSH receptor antibodies (TSHR-Abs); (ii) excessive synthesis and secretion of thyroid hormones, autonomously produced by constitutively activated malignant thyroid cells (malignant AFTN); (iii) excessive thyroid hormone secretion due to increased malignant thyroid tissue mass as in the case of bulky metastases of differentiated thyroid carcinomas and large ovarian teratomata containing a high proportion of thyroid tissue (struma ovarii). In these cases hyperthyroidism might occur after an iodine load.

Among these conditions the association of thyroid cancer and Graves' disease has recently emerged as particularly intriguing for several aspects: (a) the frequency of the association (which was considered very rare); (b) the possible increased cancer aggressiveness and consequent clinical implications; (c) the pathogenic mechanism(s) that may promote thyroid neoplastic transformation in Graves' disease.

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Prevalence of thyroid nodules and thyroid cancer in Graves' patients

Thyroid nodule prevalence

Thyroid nodules are a common finding in the general population. Community-based epidemiological surveys carried out by thyroid palpation have found a thyroid nodule prevalence of 3·2–4·7% in people living in iodine-sufficient areas, such as the USA (Vander *et al*., 1968). Nodules are two- to threefold more frequent in endemic goitre areas where iodine intake is moderately deficient (Belfiore *et al*., 1987). Nodule prevalence tends to increase with age and is higher in women than in men. In Graves' patients the prevalence of palpable thyroid nodules is approximately threefold higher than in the general population. In a cooperative study involving 36 050 patients treated for hyperthyroidism in 26 institutions, Dobyns *et al*. (1974) reported a palpable nodule prevalence of 15·8% in Graves' patients. A similar nodule prevalence has been reported by Pacini *et al*. (1988) (165 patients with nodules among 1223 Graves' patients) and by Carnell and Valente (1998) (60 patients with nodules out of 468 Graves' patients).

A much higher thyroid nodule prevalence has been found in epidemiological studies when sonography was used to examine thyroid morphology. By using this technique, Brander *et al*. (1991) found a prevalence of 27·3% in a random population sample from a non-endemic area. A similar prevalence (25% and 42% in subjects younger or older than 50 years, respectively) was found by Bruneton *et al*. (1994). In close agreement with these values, several autopsy studies have provided estimates of thyroid nodule prevalence ranging from 40 to 50% (Mortensen *et al*., 1955; Oertel & Klinck, 1965).

To our knowledge, systematic ultrasound surveys have seldom been reported in Graves' patients. In one study, 315 consecutive Graves' outpatients were studied by ultrasonography. Thyroid nodules larger than 8 mm were detected in 106 (33·6%) patients; in 44 of these patients nodules were palpable. Interestingly, in more than half these patients ($n = 57$) a thyroid nodule developed during follow-up, suggesting that Graves' disease is associated with nodule development (Cantalamessa *et al*., 1999).

Although further studies comparing Graves' and controls are needed, it seems that not only palpable nodules but also small non-palpable nodules are more frequent in Graves' patients

than in euthyroid subjects and that Graves' disease is associated with *de novo* nodule formation.

Thyroid cancer prevalence

Thyroid cancer is an infrequent malignant tumour accounting for 1–2% of all cancers and with an incidence ranging from 0·5 to 10 per 100 000 (Scottenfeld & Gershman, 1977; Franceschi & La Vecchia, 1994). Approximately 90% of thyroid carcinomas originating from the follicular epithelium are represented by well-differentiated tumours with papillary or follicular histotype while approximately 10% of all thyroid carcinomas are represented by undifferentiated tumours (Mazzaferri, 1993b). Iodine intake might influence cancer histotype in the population. Follicular carcinomas are observed mainly in iodine-deficient areas whereas papillary carcinomas account for 80–90% of differentiated carcinomas in iodine-sufficient areas. It is generally believed that only a small proportion of clinical papillary thyroid cancers develops from benign thyroid lesions while most of them arise *de novo*, progressing to clinically evident disease from small, clinically inapparent (occult) thyroid cancers. However, occult cancers are commonly found at autopsy examination of the thyroid gland with a prevalence ranging from 4·5 to 356 per 1000, indicating that only a small proportion of these lesions progresses to a clinical disease (Wang & Crapo, 1997).

Several lines of evidence indicate that Graves' patients might have an increased prevalence not only of benign thyroid nodules but also of differentiated thyroid carcinomas, mainly of the papillary histotype, suggesting therefore that Graves' disease stimulates occult cancer progression to a clinical disease. Evidence comes from three different types of studies.

Studies in Graves' out-patients series. These studies have reported an increased prevalence of clinical thyroid cancer. In a series of 468 Graves' patients, Carnell and Valente (1998) reported six differentiated cancers with a frequency of 1·3%. We reviewed the cancer frequency in a series of 920 Graves' patients observed in the period 1982–94 in an out-patient setting. In the 450 patients who underwent surgery, 36 differentiated thyroid cancers were diagnosed (3·9%), 21 (2·3%) non-occult and 15 (1·6%) occult; 91·4% were papillary carcinomas (Pellegriti *et al*., 1998).

Surgical series of Graves' patients. The reported frequency of histological diagnosis of thyroid cancer in Graves' patients undergoing thyroidectomy is highly variable, ranging from 0 to 9·8% (Table 1). The reasons accounting for these discrepancies

Table 1 Histological diagnosis of thyroid cancer in Graves' patients and in Graves' patients with clinically evident thyroid nodules.

Reference	No. patients studied	% Cancer in Graves' patients	% Cancer in Graves' patients with clinical nodules
Shapiro *et al*., 1970	172	8·7	
Dobyns *et al*., 1974	100	0·4	13
Hancock *et al*., 1977	457	1·5	
Wahl *et al*., 1982	178	1·1	
Farbota *et al*., 1985	117	5·1	
Behar *et al*., 1986	194	5·2	
Pacini *et al*., 1988	86	6·9	22·2
Rieger *et al*., 1989	64	0	
Ozaki *et al*., 1990	743	2·6	
Belfiore *et al*., 1990	132	9·8	45·8
Hales *et al*., 1992	886	1·8	5·8
Terzioglu *et al*., 1993	33	6·0	
Chou *et al*., 1993	674	1·5	
Miccoli *et al*., 1996	140	9·3	
Pomorski *et al*., 1996	704	0·4	
Pellegriti *et al*., 1998	450	4·7 (clinical) 3·3 (occult)	
Kraimps *et al*., 1998	110	5·5	21·4
Carnell and Valente, 1998	468	1·3	10
Cantalamessa *et al*., 1999	315	0·3	2·3
Kraimps, 2000	557	3·8	15

Data before 1970 are not included.

are unclear and might include differences in the genetic background and/or unidentified environmental factors. It must be considered, however, that all these studies are retrospective and might cover a very long period during which the criteria for patient selection (i.e. systematically operated Graves' patients *vs*. Graves' patients operated for a nodule), the extension of thyroidectomy and the accuracy of pathological examination have changed significantly. In a recent multicentre study carried out in Europe (557 consecutive patients who underwent operation for Graves' disease in the period 1991–97) a differentiated thyroid cancer was found in 21 patients (3·8% of all patients and 15% of patients with a nodule). Tumour size ranged from 2 to 25 mm and only four tumours were palpable (Kraimps *et al*., 2000) (Table 1).

Studies on the malignancy rate of thyroid nodules. The malignancy rate of palpable thyroid nodules in Graves' patients is reported to range from 2·3 to 45·8% (mean = 16·9%) (Table 1) while the malignancy rate of palpable nodules occurring in the general population is approximately 5% (Belfiore *et al*., 1992; Mazzaferri, 1993a). Furthermore, a palpable nodule is present in 10–15% Graves' patients but only in approximately 5% of the general population (see above). From these figures it seems that malignant nodules are present in 1·7–2·5% of Graves' patients but in only 0·25% of the general population, i.e. 6·8–10 times less than in Graves' patients.

Taken together, these studies indicate that the prevalence of clinical thyroid cancer is increased in Graves' patients and a thyroid nodule diagnosed in Graves' patients is at higher risk for malignancy, as compared to euthyroid patients.

Clinical course of thyroid cancer in Graves' patients

Most differentiated thyroid carcinomas (DTCs) have a relatively indolent course and remain confined to the thyroid gland or spread to loco-regional lymph nodes (Mazzaferri, 1993b). Only approximately 10% of DTCs develop distant metastases or critical invasion of extrathyroid structures and cause the patient's death. One important question is whether Graves' disease affects the clinical course and the outcome of differentiated thyroid cancer.

This issue has yielded contrasting results. In many studies no direct comparison was made with euthyroid patients as control. Thus, thyroid cancer was described as unusually aggressive in 20 cases reported by Behar *et al*. (1986); eight patients presented either nodal or distant metastases or muscle invasion, and two patients died from cancer. Furthermore, Ozaki *et al*. (1990) reported 19 cases characterized by frequent invasive growth in the surrounding thyroid tissue and nodal metastases. Other authors, in contrast, did not find a more aggressive course of thyroid cancer in Graves' patients (Pacini *et al*., 1988; Hales *et al*., 1992).

To our knowledge, only two groups have compared the clinical characteristics of thyroid cancer occurring in Graves' patients and euthyroid controls. We described 13 cases of cancer associated with Graves' disease (Belfiore *et al*., 1990). They showed nodal and distant metastases, invasive growth and bilateral foci more frequently than cancer diagnosed in euthyroid patients. In a subsequent study we compared the long-term outcome of 21 clinical cases of thyroid cancer associated with Graves' with that of thyroid cancer in euthyroid patients matched for age, sex and tumour size (Pellegriti *et al*., 1998). At diagnosis, Graves' patients had distant metastases more frequently than matched euthyroid controls. In Graves' patients, tumours also had a less favourable outcome as judged by persistent disease and cancer-related deaths ($P = 0{\cdot}0071$). The cumulative risk for recurrent/progressive distant metastases was approximately threefold higher in Graves' patients than in euthyroid patients (odds ratio = 3·14). Occult cancers ($n = 15$) did not behave aggressively.

Hales *et al*. (1992) described 16 cases of thyroid cancer associated with Graves' disease. They observed no difference in cancer progression with respect to age- and sex-matched euthyroid patients. However, in this series the size of tumours in Graves' patients was significantly smaller than in the euthyroid group (0·91 ± 1·2 *vs*. 2·33 ± 1·7 cm) with only two cancers in the Graves' group having a size greater than 1·0 cm, suggesting the possibility that in this study occult cancers of Graves' patients were compared to non-occult tumours in euthyroid patients.

These studies suggest that it is reasonable to consider concomitant Graves' disease to be a negative prognostic factor in a patient with a differentiated thyroid cancer (Mazzaferri, 1990), although further studies are needed to definitively prove it.

As TSH stimulates growth of metastatic differentiated thyroid cancer expressing the TSH receptor (TSHR), it is possible to hypothesize that high levels of the anti-TSHR antibodies of Graves' patients might stimulate thyroid cancer growth and early metastatic spread, thus negatively affecting patient outcome. This hypothesis will be further discussed in the last section.

Thyroid cancer after Graves' disease treatment with radioactive iodine

Radioactive iodine (RAI) administration is an effective and extensively used therapy for Graves' disease, especially in the USA. As radiation is a known carcinogenic factor for the thyroid, several studies have been carried out to assess whether RAI administration at doses used to treat hyperthyroidism increases the risk of thyroid cancer. No firm conclusion,

however, has been reached. Early studies (Dobyns *et al*., 1974) indicated that thyroid cancer incidence and mortality are not significantly increased in Graves' patients treated with RAI compared to patients treated with other therapies. More recently, Ozaki *et al*. (1994) reported in RAI-treated Graves' patients a lower cancer incidence than in Graves' patients treated with surgery (0·17% *vs.* 2·5%). Furthermore, most thyroid carcinomas that developed in RAI-treated Graves' patients were small, suggesting that after RAI treatment, subsequently occurring thyroid carcinomas have a less aggressive phenotype (Ozaki *et al*., 1994).

In contrast, reports of some anaplastic carcinomas occurring after RAI therapy have led to the hypothesis that radioiodine administration might favour progression from differentiated to undifferentiated carcinomas (Fujikawa *et al*., 1998). Recently, in a mortality study including 30 725 Graves' patients from the original Cooperative Thyrotoxicosis Therapy Follow-up Study (Ron *et al*., 1998), mortality for thyroid cancer was increased compared to that expected on the basis of death rates in the general population. The standardized mortality ratio (SMR) was 2·84 (95% CI = 1·62–4·61). However, this difference was not significant after 5 or more years of follow-up (SMR = 1·88; 95% CI = 0·86–3·57), as described by Hall *et al*. (1992), who found an SMR of 3·33 (95% CI = 1·54–5·98) that disappeared after 10 years.

Taken together, these studies suggest that radioiodine therapy for Graves' disease is a safe treatment, not associated with a significant increase in total cancer mortality, although it might be associated with an increased incidence of thyroid cancer. Mortality studies, however, might underestimate the real incidence of thyroid cancer, which has an indolent course in most cases. Also, these studies are not able to indicate whether the increased thyroid cancer incidence is due to the carcinogenic effect of RAI or is, at least partially, due to the late growth of small carcinomas already present and overlooked at the time of RAI administration to the Graves' patients. However, these data underline the need to evaluate accurately the existence of thyroid nodules before treating a Graves' patient with RAI.

Graves' disease in patients who had undergone total thyroidectomy for thyroid cancer

Persisting circulating TSAb after total thyroidectomy

Thyroid stimulating antibodies (TSAbs) have been hypothesized to play a role in thyroid cancer promotion, since they stimulate thyroid cells via the TSHR (Filetti *et al*., 1988). Systematic studies regarding the persistence of TSAbs after total thyroidectomy are lacking. Intrathyroid lymphocytes are believed to be the major source of anti-TSHR antibodies and a progressive decrease of the TSAb titre has been described in Graves' patients after subtotal or total thyroidectomy.

We know that in certain patients, TSAbs might persist for a long time after thyroidectomy. In a series of 12 Graves' patients who underwent total thyroidectomy for thyroid cancer, 11 patients had serum TSAb still detectable after 9–72 months (Belfiore *et al*., 1990). Nakamura *et al*. (1992) reported a case with both TSAb and thyroid stimulation blocking antibodies (TSBAbs) apparently unchanged up to 16 months after total thyroidectomy. As the half-life of circulating IgG is 7–23 days, these data indicate that extrathyroid lymphocytes might also contribute to produce thyroid antibodies. Some of these patients might have small thyroid remnants or small cancer foci at the level of loco-regional lymph nodes that provide a continuous antigenic stimulus.

Development of Graves' disease after total thyroidectomy for thyroid cancer

Some reports have shown that Graves' disease might relapse or develop *de novo* several years after total thyroidectomy for thyroid cancer (Filetti *et al*., 1988; Steffensen & Aunsholt, 1994). In these cases clinical signs of Graves' disease and the appearance of TSAbs have been coincident with a rise in serum thyroglobulin levels and evidence of cancer recurrence. These data strongly suggest that the presence of even small foci of cancer tissue might be sufficient for triggering Graves' disease, which might, in turn, promote cancer relapse. The frequency of this phenomenon is unknown and probably very low. However, the development of Graves' disease in patients who had undergone total thyroidectomy might be overlooked in the absence of ophthalmopathy. To our knowledge, no study has evaluated the prevalence of circulating TSAbs in patients with metastatic and/or recurrent thyroid cancer. Further studies are required to assess the impact of persisting or *de novo* appearance of high titres of TSAbs in patients operated on for thyroid cancer and with tumour recurrence.

Clinical implications of the association of Graves' disease with thyroid cancer

The treatment options for Graves' disease are essentially three: (a) thyroidectomy; (b) radioactive iodine; and (c) medical treatment with anti-thyroid drugs. The initial therapeutic choice for Graves' patients is influenced by the local context (medical/surgical expertise, nuclear medicine facilities), by economic considerations and stringency of safety rules for radioiodine use (Caruso & Mazzaferri, 1992). Radioiodine treatment is preferred in the USA and thyroidectomy is preferred in most European and Asian countries (Escobar-Jimenez *et al*., 2000), while anti-thyroid drugs are mostly used as preparation for final therapy.

From the clinical point of view, the initial choice of treatment is based on the following parameters: goitre size, surgical risk, patient age and preferences, and pregnancy status (Caruso & Mazzaferri, 1992).

The data on thyroid cancer association with Graves' disease have two major implications. First, the presence of concomitant thyroid nodules might be regarded as a factor for choosing the most appropriate initial treatment. Non-palpable nodules represent approximately 90% of all thyroid nodules and even nodules larger than 2 cm located deeply or in the context of a goitre often escape detection at physical examination by an experienced clinician (Wiest *et al*., 1998). Therefore, we suggest that Graves' patients should undergo an accurate examination of the thyroid gland not only by palpation but also by ultrasound, and if a thyroid nodule is found at ultrasound it should always be examined by fine-needle aspiration biopsy (FNAB). Furthermore, given the suggestion of an increased cancer risk in nodules concomitant with Graves' disease, we think it is reasonable to recommend a low threshold for nodule referral to surgery, unless FNAB examination by an expert cytologist makes the diagnosis of cancer highly unlikely.

Second, the presence of TSAbs might affect surgical and/or postsurgical thyroid cancer management in patients with Graves' disease. Two different conditions can be identified: (a) thyroid cancer patients with pre-existent Graves' disease; and (b) the appearance of TSAbs and/or clinical Graves' disease during follow-up of patients previously operated on for thyroid cancer and with no pre-existing manifestations of Graves' disease.

As reported above, the first condition is not infrequent, with clinical thyroid cancers occurring in 3–7% of patients with Graves' disease. Although further studies are needed to confirm that concomitant Graves' disease increases the risk for cancer recurrence and/or metastases in thyroid cancer patients, we believe that a total or near-total thyroidectomy plus loco-regional lymph node resection should be the treatment of choice. It would probably be wise to carry out the postsurgical follow-up of these patients according to the protocol used for high-risk patients.

The development of Graves' disease in patients who had undergone thyroidectomy for thyroid cancer is rare. Nonetheless, when thyrotoxicosis or ophthalmopathy develops in these patients, thyroid antibodies including TSAbs should be measured. If the diagnosis of Graves' is made, it should be regarded as an additional risk factor for cancer recurrence and/or aggressiveness.

The TSHR as a proto-oncogene and the anti-TSHR antibodies as promoting factors of malignant transformation

Graves' disease is currently viewed as an autoimmune disease in which a major pathogenic role is played by activating antibodies (TSAbs) to the TSHR, able to stimulate thyrocyte growth and function. As most thyroid nodules, including malignant ones, retain TSHR expression (Ohta *et al*., 1991; Bronnegård *et al*., 1994; Potter *et al*., 1994), the possibility exists that a growth-promoting effect might result by TSAb binding to the nodule TSHRs, especially in thyrocytes hosting somatic genetic/epigenetic alterations predisposing to nodular growth. It is well known that the TSHR is highly susceptible to undergoing structural modifications responsible for constitutive activation. In fact, spontaneously occurring activating mutations of the TSHR gene are the cause of a number of autonomous functioning thyroid adenomas (Russo *et al*., 1997a; Duprez *et al*., 1998), although only rarely have they been described in either hyperfunctioning or hypofunctioning thyroid carcinomas (Russo *et al*., 1995, 1997b, 1999; Spambalg *et al*., 1996; Esapa *et al*., 1997; Cetani *et al*., 1999; Camacho *et al*., 2000).

However, no abnormalities in the TSHR gene have been detected in Graves' disease and a recent linkage study (DeRoux *et al*., 1996) has rejected the hypothesis that TSHR might be a major genetic determinant in this disease. Nevertheless, the functional properties of the mutant TSH receptors might help to shed light on the mechanisms involved in the association between Graves' disease and thyroid nodules and cancer. As different G-protein-coupled transduction pathways are recruited by TSHR activation (Allgeier *et al*., 1994), different mutations might predominantly activate either the cAMP or the Ca-PI pathway (Van Sande *et al*., 1995) and produce different biological effects.

TSAbs are heterogeneous and bind to different epitopes of the TSHR (Rees Smith *et al*., 1988; Rapoport *et al*., 1998). Thus, the variety of interactions between TSAbs and the TSHR might reproduce the effects of the different activating mutations in terms of conformational changes of the receptor, with signalling pathways activated differently and resulting in different effects on thyroid growth and function (Huber *et al*., 1991; Kashima *et al*., 1996).

TSAbs might also promote thyroid cell growth and survival by indirect mechanisms. One mechanism is the activation of the IGF system. TSH upregulates the expression of insulin receptors (IRs) in human thyrocytes (Van Keymeulen *et al*., 2000) and IRs might effectively transduce IGF-II effects (Frasca *et al*., 1999). Moreover, IR upregulation increases IR/IGF-I-R hybrid receptors that bind both IGF-I and IGF-II (Belfiore *et al*., 1999; Vella *et al*., 2001). In addition, TSAbs stimulate angiogenesis by upregulating vascular endothelial growth factor (VEGF) and its cognate receptor (flt) in thyroid cells (Sato *et al*., 1995).

In summary, external stimulating factors (TSAbs and other co-stimulatory factors) might cooperate with intrinsic/genetic

component(s) to favour the tumorigenic process and influence the resulting cancer phenotype in Graves' disease.

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